BACTERIOLOGICAL REVIEWS
Vol. 28, No. 4, p. 472–479 December, 1964

LATENT HERPES SIMPLEX INFECTION IN MAN[1]

THOMAS F. PAINE, JR.

Department of Medicine, Nashville General Hospital, and Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee

INTRODUCTION

The biology of experimental herpes simplex infections of chick embryo cells and tissue culture cells has been clarified greatly over the past few years by the clear-cut work of Scott and associates (45, 46), Stoker and colleagues (50, 51), and others. Indeed, the detailed knowledge of the "growth curve" of herpesvirus in infected cells, from their absorption and temporary disappearance from view, to the appearance of new virus particles in the cell nucleus, then in the cytoplasm, and again into the medium, might lead one to believe that the secrets between this virus and man are now understood. But, wait! There is still an intriguing mystery regarding this virus—a mystery which might have been foretold in these ancient words:

There be four things which are little upon the earth but they are exceeding wise;
The ants are a people not strong, yet they prepare their meat in the summer;
The conies are but a feeble folk, yet make they their houses in the rocks;
The locusts have no king, yet go they forth all of them by bands;
The spider taketh hold with her hands, and is in kings' palaces (Proverbs 30:24–28)

And the herpes virus labors not, yet lives warm and rent-free . . . . might be added to these words from the Proverbs. All these little creatures have in common a superb adaptation to a hostile world and have outlived empires and the brontosaurus. It is the living in, with only occasional clues to its presence, of the herpesvirus's residence in man which is a great mystery. The mystery is increased by the involvement of a certain anatomical site—the lips, cornea, or genitalia—year after year in recurrent herpes, suggesting that the virus has picked a certain cell or group of cells for its permanent abode. How the virus arrived there and what cells contain it during latency is unknown.

[1] A contribution to the Symposium on "Current Progress in Virus Diseases" presented as part of the program for the Centennial of the Boston City Hospital, 1 June 1964, with Maxwell Finland serving as Consultant Editor, and John H. Dingle and Herbert R. Morgan as moderators.

EXPERIMENTAL INFECTION OF ANIMALS WITH HUMAN HERPES SIMPLEX VIRUS

Interest in the pathogenesis of herpes infection was stimulated by the observation that an agent from human herpetic lesions could produce infection in the eye of the rabbit after inoculation of the scarified cornea (26, 35). In some instances, the corneal infection was followed by a herpetic encephalitis (16). Although the route of invasion of the central nervous system was unknown, both the blood stream (15) and the optic nerve (34) were suggested as avenues. Subsequent studies by Goodpasture showed that superficial inoculation of the herpes virus led to herpetic encephalitis by passage of the virus along the nerves; nevertheless, infection of the central nervous system also could be produced by intravenous injection of the agent (20, 24, 25). His elegant experiments bear closer investigation. Doerr and Vöchting (16) had observed that rabbits which developed encephalitis after unilateral corneal inoculation of herpesvirus showed a curious drawing of the head towards the affected side. Goodpasture found that this neurological phenomenon was associated with unilateral

lesions in the pons and medulla which corresponded to the central distribution of the sensory fibers of the fifth cranial nerve on the inoculated side (25). A reproduction of one of Goodpasture's illustrations (Fig. 1) shows the grossly hemorrhagic lesions in such an experimentally infected rabbit. In this instance, the location of the lesions has been accentuated by the intravenous injection of trypan blue before death of the animal (37). Microscopically, acute inflammation with necrosis and infiltration with polymorphonuclear and mononuclear cells was observed, limited to the side of the pons and medulla corresponding to the gross lesions. Herpetic intranuclear inclusion bodies were seen in glial and ganglion type cells in such lesions.

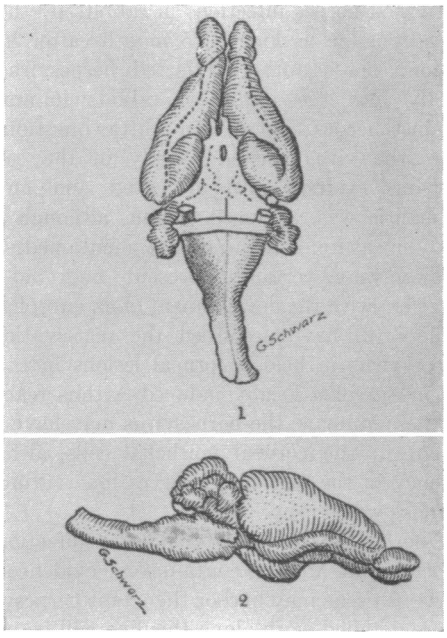

FIG. 1. *Brain of rabbit previously inoculated on right cornea with virus of herpes febrilis, showing distribution of area stained by intravenous injection of trypan blue. Area of staining is unilateral on right side, beginning in intradural part of sensory portion of fifth cranial nerve and following the distribution of these fibers through pons and medulla (reproduced from J. Med. Res.* **44**:*206, 1923*).

Goodpasture demonstrated passage of herpesvirus to the central nervous system in rabbits via the three principal nervous pathways (25). To illustrate transmission along sensory nerves, he inoculated the virus upon the right cornea; the virus passed along sensory fibers of the right fifth cranial nerve, producing local unilateral lesion in pons and medulla (right side) which corresponded to the distribution of sensory fibers of this nerve. Another experiment showed passage along motor nerves. In this experiment, he found that virus inoculated into the right masseter muscle causes an encephalitis localized in pons and medulla, with infection in and destruction of ganglion cells in the motor nucleus of the right fifth cranial nerve. To show passage along sympathetic nerve fibers, virus was inoculated into the left ovary, producing complete paralysis of the caudal half of the body, and acute herpetic myelitis of the midthoracic segment of the spinal cord. These experiments led Goodpasture to conclude that the virus of herpes labialis, when inoculated into rabbits in the different sites mentioned, could reach the central nervous system via sensory, motor, or sympathetic nerves. The initial injury in the brain or spinal cord arose at the point where the nerves which supply the peripherally inoculated area entered the central nervous system. After entry into the brain, the virus might then spread, producing a generalized encephalitis. That the virus traveled via the peripheral nerves was further supported by studies showing that the lumbar spinal cord myelitis produced by inoculation of the agent into a leg muscle supplied by the sciatic nerve did not occur if the sciatic nerve was severed before inoculation. Goodpasture also noted that herpes strains varied in neurotropic virulence and that rabbits varied in their natural resistance to invasion of the central nervous system by this virus (22).

The neurotropism of herpesvirus was later confirmed in the chick embryo by Anderson (1) and in the mouse by Slavin and Berry (47). Goodpasture (25) postulated that transmission of virus along the peripheral nerves occurred within the axons. Viral involvement of some neuroglial cells outside of the axis cylinders but still inside the myelin sheath was interpreted as resulting from escape of virus in places along the axons. A recent study by Johnson (30) with the use of a fluorescent-antibody staining technique in experimentally infected suckling mice provided good evidence that the herpesvirus is transmitted in peripheral nerves through infected Schwann cells and perineural fibroblasts rather than in the axis cylinders. Invasion of the sensory ganglia

seemed to take place when the level of advancing infection in the neuroglial cells reached the ganglia. Axonal spread in addition to spread of the virus through the neuroglial cells was not entirely excluded, since the serum-conjugate system used in the indirect fluorescent-antibody staining technique failed to stain herpetic material in the nuclei of cells (33, 42, 43) and may have failed to stain a form of the virus present in the axons.

The natural spread of herpesvirus among rabbits provides another clue regarding the neurotropism of this agent. Goodpasture (21) placed normal rabbits in cages with rabbits shedding purulent material from experimental herpetic keratitis. The majority of normal rabbits exposed developed herpetic encephalitis. The earliest inflammatory lesions in the central nervous system of the exposed animals were found to involve the origins of the sensory divisions of the fifth and the ninth cranial nerves, indicating a primary infection of cells in the mucosa of the mouth, nose, or throat, followed by spread through the sensory nerves from the infected tissue to the central nervous system.

Generalized herpetic infections with widespread involvement of many organ systems can be produced in experimental animals, particularly in the young (1, 30, 47), and have been observed in young children (3). In this respect, the herpes virus is no different from many other infectious agents which ordinarily infect one organ system but occasionally produce overwhelming systemic infections. In summing up the evidence from experimental herpes infections in animals, it seems safe to conclude that, after superficial inoculation in animals, the human herpes simplex virus shows a remarkable preference for nervous tissue as a place for growth and infection.

LATENT HERPETIC EXPERIMENTAL INFECTIONS IN ANIMALS

Since the latent state of the herpesvirus in humans was recognized, several attempts have been made to produce latent infections in experimental animals. Good and Campbell (19) reported the activation of herpes infection in rabbits 1 to 3 months after inoculation by producing an anaphylactic reaction with egg white. The original inoculation of virus was made into the quadriceps muscle. Activation of herpetic infection took the form of an acute myelitis and encephalitis appearing about 5 days after the anaphylactic reaction. Although antibody measurements in the rabbits were not mentioned, it is reasonable to assume the presence of antibodies 1 to 3 months after viral inoculation. The antibodies apparently did not interfere with the development of the encephalitis, suggesting that the herpes organisms may well have been present in a latent state in cells free from the inhibiting effect of antibodies. Schmidt and Rasmussen (44) activated herpes infections in rabbits by the use of adrenaline as long as 5 months after inoculation. These authors injected herpesvirus directly into the brains of rabbits immunized against herpes. There seems little question but that the virus existed quietly in the central nervous system until activated and an encephalitis was produced. Again, although antibody measurements were not mentioned, antibodies were certainly present and did not interfere with the development of an encephalitis. Others (2) have described the reactivation of herpesvirus in healed corneal lesions in rabbits by means of a locally induced Arthus reaction; in these animals, the herpesvirus may have been latent in the corneal epithelial cells, although latency in the peripheral nerves innervating the corneas was not excluded.

The few reports on latent herpes infections in experimental animals contain some evidence that nervous tissue may harbor the latent herpesvirus. More detailed work along this line will be necessary to determine whether prolonged latency can be produced in animals and what tissues serve as a residence of the virus during latency.

EVIDENCE FOR LATENT HERPESVIRUS IN NERVOUS TISSUE IN MAN

Most adults harbor herpes simplex virus (8). The oropharynx is considered the usual place of primary infection (8, 14), with no immediate indication of involvement of nerves supplying this area. Latency, as indicated by recurring vesicles on the lips, usually shows no evidence of a distribution corresponding to peripheral nerve fibers. There is, however, evidence linking the herpesvirus to nervous tissue in man. Early reports by Cushing (11, 12, 13) concerning the surgical treatment of trigeminal neuralgia offered the first clues. His observations, coupled with later experience with herpes activation by surgery for tic douloureux, have shown that: (i) labial

and facial herpetic lesions appear postoperatively in a high percentage of patients undergoing posterior root section of the fifth cranial nerve—as high as 93% in one series reported by Carton (9); (ii) the herpetic lesions occur on the same side on which the fifth nerve root is sectioned (9); (iii) the herpetic lesions appear usually in the skin or mucosal innervation areas of the second and the third divisions of the sectioned fifth nerve (10); (iv) herpetic lesions do not appear after interruption of the peripheral divisions of the fifth cranial nerve (9); (v) interruption of the second and third peripheral divisions of the trigeminal nerve before subsequent root section prevents the appearance of herpetic lesions which usually follow such a procedure (9); and (vi) destruction of the Gasserian ganglion, by the injection of alcohol into the ganglion, usually is not followed by the appearance of herpetic lesions (9). These observations show that disturbing the posterior sensory root of the fifth cranial nerve by operation results in the appearance of herpetic vesicles in the areas innervated by the second and third peripheral divisions of the nerve in a highly significant number of patients, provided the ganglion has not been destroyed and the peripheral divisions are intact.

Other significant observations linking peripheral nerves with herpes simplex virus have been summarized and substantiated by Slavin and Ferguson (48). Some patients with recurring herpetic vesicles show a distribution of lesions corresponding to peripheral nerves. These patients may have involvement of the trigeminal area as well as other dermatomes in a zoster-like fashion. Recurring neuralgic pain in the innervation pattern of the involved area may be noted prior to the appearance of the vesicles, and may indicate a posterior root involvement by the virus. Herpes simplex virus was clearly isolated by Slavin and Ferguson (48) from the vesicles of a series of patients with recurring zosteriform lesions. It is of interest that Teague and Goodpasture (52) reported the production of zosteriform lesions in rabbits and guinea pigs with human herpes simplex virus by irritating the skin with coal tar and inoculating the virus nearby. These studies indicated a centripetal spread of the virus from the inoculated site via peripheral nerves to the sensory ganglia, followed by a centrifugal spread of the agent with the appearance of vesicles in the area of the irritated skin.

Since Goodpasture's early postulate (23) suggesting the Gasserian ganglion as a likely site for the residence of latent herpesvirus, this anatomical structure has been the prime suspect for harboring the virus. The few reported (7, 10, 18, 41) unsuccessful attempts to isolate virus from Gasserian ganglion removed at operation by no means eliminate this structure as a storage site for the agent. The herpesvirus particle is now known to consist of a core imbedded in a shell and surrounded by an envelope (56). Perhaps the core of the virus is present during latency but lacks the shell or envelope to make it a complete infective unit (36). Electron microscopic evidence suggests that there is a structural difference between intranuclear and intracytoplasmic herpes particles (38). Herriott has suggested that the herpesvirus may exist as a free deoxyribonucleic acid (27). Thus, the latent virus may be present in neural tissue in a form similar to that existing during the eclipse phase (46) in tissue culture when active virus temporarily can not be isolated.

Other clues linking herpes and the fifth cranial nerve in man are not very definitive. Howard (28, 29) noted gross and microscopic inflammatory changes in the Gasserian ganglia in autopsy studies on two patients with labial herpetic-like lesions; one patient had succumbed with bacterial pneumonia and the other with typhoid and staphylococcal pneumonia. Inflammatory infiltrations in the Gasserian ganglion in three patients were described by Freeman, as quoted by Richter (41). Behrman and Knight (4) discussed three patients in whom recurrent neuralgia of branches of the trigeminal nerve was followed by the appearance of herpetic-like lesions in areas innervated by the involved nerve branches; this repetitive association suggested a relationship between the recurrent neuralgia of the trigeminal nerve and the herpes virus. Another clue suggesting nervous tissue latency was the appearance of herpetic lesions almost entirely in areas innervated by the second and third divisions of the trigeminal nerve (32) in a high percentage of adult patients given fever therapy when this method of treatment was in vogue. The occasional recurrence of herpes simplex vesicles in a zoster-like distribution and the high rate of activation of herpesvirus by operations on the posterior sensory root of the fifth cranial nerve

in patients with trigeminal neuralgia suggest that the herpesvirus may be present in its latent state in nervous tissue. The virus could be present in neurones or in neuroglial cells in the sensory ganglia or in peripheral nerves in Schwann or other cells within the myelin sheath. Definite proof awaits isolation of the virus from these structures or demonstration of the latent form in situ.

EVIDENCE FOR LATENT HERPESVIRUS OUTSIDE OF THE NERVOUS SYSTEM IN MAN

The commonly recurring epithelial herpetic vesicles, with no apparent relationship to peripheral nerves, may indicate a superficial residence of the herpesvirus between attacks. The latent virus could be present in the basal germinative layer of epithelial cells, with the viral nucleic acid being passed down to later generations of germinative epithelial cells, as in the transfer of bacteriophage nucleic acid to new generations of bacterial cells. Indeed, the shedding of herpesvirus in the saliva for several weeks after primary infection and the occasional finding of the virus in the saliva of apparently normal adults (6) might be taken as evidence for a superficial residence of the virus. However, it is equally reasonable to believe that the latent virus lives in superficial nerve endings, spreading to the epithelial cells when activated. Epithelial tissues, including the mucous membranes and cornea, contain a rich variety of sensory nerves; these include networks of free sensory nerve endings, corpuscles of Vater-Pacini, nonencapsulated nerve glomeruli, genital corpuscles, and Meissner's corpuscles (5). One report, however, states that areas of facial skin subject to recurrent herpes did not continue to manifest herpetic lesions if transplanted to another site on the body (49).

The presence of residual islands of latent herpesvirus in the skin and mucosa has been suggested as an explanation for the appearance of herpetic vesicles in the distribution of the second and third peripheral divisions of the trigeminal nerve after posterior sensory root section of all three branches. This view has been advanced on the thesis that if herpesvirus were activated while residing in the Gasserian ganglion it should spread to all peripheral branches of the fifth nerve (10). However, the latent herpesvirus may be associated only with the neurones innervating the site of original infection, a phenomenon noted by Goodpasture (21) in his study of the natural spread of herpes infection in caged rabbits. The oral cavity in man, innervated by the maxillary and mandibular branches of the fifth cranial nerve, is the usual site of primary infection. Further, there is no reason to believe that common neurones in the Gasserian ganglion serve all three peripheral branches of the trigeminal nerve. In man's embryological development, the fifth nerve results from fusion of the sensory ganglia of two nerves, the ophthalmic, emerging in front of the second myotome, and the maxillo-mandibularis, emerging behind the second myotome (31). Thus, while occupying a common structure, the Gasserian ganglion, the neurones innervating the ophthalmic division are probably quite distinct from those innervating the maxillary and mandibular divisions.

CONCLUSIONS

The life-long secret residence of the herpesvirus in man is still unknown. Clinical evidence suggests that the site relates to the point of primary infection, usually the mouth or lips. Experimental studies in animals and activation of latent infections in man after operation for trigeminal neuralgia indicate a distinct neurotropism of the herpes simplex virus. Although the original infection in epithelial cells may lead to deposition of viral nucleic acid in the basal germinative layer of these cells, the definite neurotropism of the virus suggests that primary infection of man results in invasion of superficial nerve endings, and thereafter the viral nucleic acid remains in neural tissue. Peripheral nerve cells are remarkable in their size and make-up, having nuclei situated near the central nervous system while their cytoplasm extends many inches or even feet distant from their nuclei. Viral nucleic acid taking refuge in nervous tissue would find a secure residence. These cells are not undergoing constant new cell formation; thus, the risk of being misplaced or lost while being transferred to daughter cells, as in an epithelial cell residence, is decreased. Perhaps it is a coincidence, but there is a similarity in time of transmission of herpesvirus from the cornea to the brain of a rabbit (72 to 96 hr; 25) and the time required for the expression of peripheral herpes in man following posterior sensory root section in cases of trigeminal neuralgia (48 to 96 hr; 10). Cen-

trifugal spread of the virus along nerves was early demonstrated by Teague and Goodpasture (52), and in the case of man this time could represent the period needed for migration of the viral nucleic acid from a central location in the nerve to the peripheral nerve endings in the epithelium. Nerve cell nuclei would be likely structures to synthesize new infective virus particles from the latent state. The participation of nuclei of tissue culture cells in production of herpesvirus has been demonstrated clearly (33, 38, 39, 40, 42, 43). Synthesized virus might travel centrifugally in nerves in a manner first suggested by Weiss (53, 54), who proposed that the axon material of the nerve was produced in the region of the nucleus and moved away from the nucleus into the peripheral nerves. A recent note (55) confirms this hypothesis and offers visual proof of a constant movement of axonal material and of mitochondria from the nucleus of the nerve into the peripheral axon. Droz and Leblond (17), using tritium-labeled leucine, demonstrated the synthesis of new protein in the rat sciatic nerve cell nucleus and showed a centrifugal progression of the labeled protein in the axon of the nerve in radioautographic studies. The rate of progression of the labeled protein was not fast enough to account for the appearance of herpetic vesicles in the skin after section of the posterior sensory root of the trigeminal nerve if the virus had to progress from the Gasserian ganglion at the same rate as the labeled protein. However, under different circumstances virus particles might move in the axon at a different rate of speed. Weiss (55) recently described visible peristaltic waves occurring in myelinated sensory nerves in vitro. The rate of peristaltic activity in nerve fibers probably depends upon the metabolic situation in the nerve. An increased speed of centrifugal axonal flow could result if nerve fiber peristalsis increased because of metabolic changes in the fifth cranial nerve from the "irritation" of the sectioning of its posterior sensory root.

Based on presently available information, the following hypothesis for the pathogenesis of latency of herpes simplex virus in man is suggested. (i) Primary infection probably involves sensory nerve endings in addition to epithelial cells. (ii) The virus travels centripetally in sensory nerves through contiguous endoneural supporting cells, particularly the Schwann cells. (iii) Ganglionic nerve cell nuclei are invaded when the centrally moving infection of the neuroglial cells reaches the level of the ganglia. (iv) The noninfective core of the herpesvirus may remain in its latent state in the sensory ganglia, usually the Gasserian ganglia. (v) On activation of the herpesvirus, new infective virus particles may be synthesized in the nerve cell nucleus and released into the cytoplasm of the nerve. (vi) By means of an axonal flow due to nerve fiber peristalsis, the infective virus particles move in a centrifugal direction down the axon of the peripheral nerve until epithelial cells are reached, where the characteristic vesicles are produced.

LITERATURE CITED

1. ANDERSON, K. 1940. Pathogenesis of herpes simplex infection in chick embryos. Am. J. Pathol. **16**:137–155.
2. ANDERSON, W. A., B. MARGRUDER, AND E. D. KILBOURNE. 1961. Induced reactivation of herpes simplex virus in healed rabbit corneal lesions. Proc. Soc. Exptl. Biol. Med. **107**: 628–632.
3. BECKER, W., W. DE T. NAUDE, A. KIPPS, AND D. MCKENZIE. 1963. Virus studies in disseminated herpes simplex infections. Association with malnutrition in children. S. African Med. J. **37**:74–76.
4. BEHRMAN, S., AND G. KNIGHT. 1954. Herpes simplex associated with trigeminal neuralgia. Neurology **4**:525–530.
5. BLOOM, W., AND D. W. FAWCETT. 1962. A textbook of histology, 8th ed., p. 234–237. W. B. Saunders Co., Philadelphia.
6. BUDDINGH, G. J., D. I. SCHRUM, J. C. LANIER, AND D. J. GUIDRY. 1953. Studies of the natural history of herpes simplex infections. Pediatrics **11**:595–610.
7. BURNET, F. M., AND D. LUSH. 1939. Herpes simplex. Studies on the antibody content of human sera. Lancet **1**:629–631.
8. BURNET, F. M., AND S. W. WILLIAMS. 1939. Herpes simplex: a new point of view. Med. J. Australia **1**:637–642.
9. CARTON, C. A. 1953. Effect of previous sensory loss on the appearance of herpes simplex following trigeminal sensory root section. J. Neurosurg. **10**:463–468.
10. CARTON, C. A., AND E. D. KILBOURNE. 1952. Activation of latent herpes simplex by trigeminal sensory-root section. New Engl. J. Med. **246**:172–176.
11. CUSHING, H. 1904. Perineal zoster, with notes upon cutaneous segmentation postaxial to the lower limb. Am. J. Med. Sci. **127**:375–391.

12. CUSHING, H. 1904. Perineal zoster. Johns Hopkins Hosp. Bull. **15**:172.
13. CUSHING, H. 1905. The surgical aspects of major neuralgia of the trigeminal nerve. A report of twenty cases of operation on the gasserian ganglion, with anatomic and physiologic notes on the consequences of its removal. J. Am. Med. Assoc. **44**:773–779, 860–865, 920–929, 1002–1008, 1088–1093.
14. DODD, K., L. M. JOHNSTON, AND G. J. BUDDINGH. 1938. Herpetic stomatitis. J. Pediat. **12**:95–102.
15. DOERR, R., AND A. SCHNABEL. 1921. Das Virus des Herpes febrilis und seine Beziehungen zum Virus der Encephalitis epidemica (lethargica). Z. Hyg. Infektionskrankh. **94**:29–81.
16. DOERR, R., AND K. VÖCHTING. 1920. Études sur le virus de l'herpes febrile. Rev. Gen. Ophthalmol. **34**:409–421.
17. DROZ, B., AND C. P. LEBLOND. 1962. Migration of proteins along the axons of the sciatic nerve. Science **137**:1047–1048.
18. ELLISON, S. A., C. A. CARTON, AND H. M. ROSE. 1959. Studies of recurrent herpes simplex infections following section of the trigeminal nerve. J. Infect. Diseases **105**: 161–167.
19. GOOD, R. A., AND B. CAMPBELL. 1948. The precipitation of latent herpes simplex encephalitis by anaphylactic shock. Proc. Soc. Exptl. Biol. Med. **68**:82–87.
20. GOODPASTURE, E. W. 1925. The axis-cylinders of peripheral nerves as portals of entry to the central nervous system for the virus of herpes simplex in experimentally infected rabbits. Am. J. Pathol. **1**:11–28.
21. GOODPASTURE, E. W. 1925. The pathways of infection of the central nervous system in herpetic encephalitis of rabbits contracted by contact; with a comparative comment on medullary lesions in a case of human poliomyelitis. Am. J. Pathol. **1**:29–46.
22. GOODPASTURE, E. W. 1925. Certain factors determining the incidence and severity of herpetic encephalitis in rabbits. Am. J. Pathol. **1**:47–55.
23. GOODPASTURE, E. W. 1929. Herpetic infection, with especial reference to involvement of the nervous system. Medicine **8**:223–243.
24. GOODPASTURE, E. W., AND O. TEAGUE. 1923. The transmission of the virus of herpes febrilis along sensory nerves with resulting unilateral lesions in the central nervous system in the rabbit. Proc. Soc. Exptl. Biol. Med. **20**:545–547.
25. GOODPASTURE, E. W., AND O. TEAGUE. 1923. Transmission of the virus of herpes febrilis along nerves in experimentally infected rabbits. J. Med. Res. **44**:139–184.
26. GRÜTER, W. 1920. Experimentelle und Klinische Untersuchungen über den Sog. Herpes corneae. Klin. Monatsbl. Augenheilk. **65**: 398–399.
27. HERRIOTT, R. M. 1961. Infectious nucleic acids, a new dimension in virology. Science **134**:256–260.
28. HOWARD, W. T. 1902. The pathology of labial and nasal herpes and of herpes of the body occurring in acute croupous pneumonia and their relation to the so-called herpes zoster. Trans. Assoc. Am. Physicians **17**:189–207.
29. HOWARD, W. T. 1905. Further observations on the relation of lesions of the gasserian and posterior root ganglia to herpes, occurring in pneumonia and cerebrospinal meningitis. Trans. Assoc. Am. Physicians **20**:165–172.
30. JOHNSON, R. T. 1964. The pathogenesis of herpes virus encephalitis. I. Virus pathways to the nervous system of suckling mice demonstrated by fluorescent antibody staining. J. Exptl. Med. **119**:343–356.
31. KAPPERS, C. U. A., G. C. HUBER, AND E. C. CROSBY. 1960. The comparative anatomy of the nervous system of vertebrates, including man, vol. 1, p. 381. Hafner Publishing Co., New York.
32. KEDDIE, F. M., R. B. REES, JR., AND N. N. EPSTEIN. 1941. Herpes simplex following artificial fever therapy. J. Am. Med. Assoc. **117**:1327–1330.
33. LEBRUN, J. 1956. Cellular localization of herpes simplex virus by means of fluorescent antibody. Virology **2**:496–510.
34. LEVADITI, C., AND P. HARVIER. 1920. Étude expérimentale de l'encéphalite dite léthargique. Ann. Inst. Pasteur **34**:911–972.
35. LÖWENSTEIN, A. 1919. Aetiologische Untersuchungen über den fieberhaften Herpes. Muench. Med. Wochschr. **66**:769–770.
36. LWOFF, A., T. F. ANDERSON, AND F. JACOB. 1959. Remarques sur les caractéristiques de la particule virale infectieuse. Ann. Inst. Pasteur **97**:281–289.
37. MCCLELLAN, R. H., AND E. W. GOODPASTURE. 1923. A method of demonstrating experimental gross lesions in the central nervous system. J. Med. Res. **44**:201–206.
38. MORGAN, C., S. A. ELLISON, H. M. ROSE, AND D. H. MOORE. 1954. Structure and development of viruses as observed in the electron microscope. J. Exptl. Med. **100**:195–202.
39. MORGAN, C., E. P. JONES, M. HOLDEN, AND

H. M. ROSE. 1958. Intranuclear crystals of herpes simplex virus observed with the electron microscope. Virology **5**:568–571.

40. NEWTON, A., AND M. G. P. STOKER. 1958. Changes in nucleic acid content of HeLa cells infected with herpes virus. Virology **5**:549–560.
41. RICHTER, R. B. 1944. Observations bearing on the presence of latent herpes simplex virus in the human gasserian ganglion. J. Nervous Mental Disease **99**:356–358.
42. ROIZMAN, B. 1961. Virus infection of cells in mitosis. 1. Observations on the recruitment of cells in karyokinesis into giant cells induced by herpes simplex virus and bearing on the site of virus antigen formation. Virology **13**:387–401.
43. ROSS, R. W., AND E. ORLANS. 1958. The redistribution of nucleic acid and the appearance of specific antigen in HeLa cells infected with herpes virus. J. Pathol. Bacteriol. **76**:393–402.
44. SCHMIDT, J. R., AND A. F. RASMUSSEN, JR. 1960. Activation of latent herpes simplex encephalitis by chemical means. J. Infect. Diseases **106**:154–158.
45. SCOTT, T. F. MCN., C. F. BURGOON, L. L. CORIELL, AND H. BLANK. 1953. The growth curve of the virus of herpes simplex in rabbit corneal cells grown in tissue culture with parallel observations on the development of the intranuclear inclusion body. J. Immunol. **71**:385–396.
46. SCOTT, T. F. MCN., L. L. CORIELL, H. BLANK, AND A. GRAY. 1953. The growth curve of the virus of herpes simplex on the chorioallantoic membrane of the embryonated hen's egg. J. Immunol. **71**:134–144.
47. SLAVIN, H. B., AND G. P. BERRY. 1943. Studies on herpetic infection in mice. II. The pathways of invasion of the central nervous system after intranasal instillation of virus in suckling mice. J. Exptl. Med. **78**:315–320.
48. SLAVIN, H. B., AND J. J. FERGUSON. 1950. Zoster-like eruptions caused by the virus of herpes simplex. Am. J. Med. **8**:456–467.
49. STALDER, W., AND S. ZURUKZOGLU. 1936. Experimentelle Untersuchungen über Herpes. Transplantation herpesinfizierter Hautstellen, Reaktivierung von abgeheilten, künstlich infizierten Hautstellen, Herpesbehandlung. Zentr. Bakteriol. Parasitenk. Abt. I Orig. **136**:94–97.
50. STOKER, M. G. P., AND R. W. ROSS. 1958. Quantitative studies on the growth of herpes virus in HeLa cells. J. Gen. Microbiol. **19**: 250–266.
51. STOKER, M. G. P., K. M. SMITH, AND R. W. ROSS. 1958. Electron microscope studies of HeLa cells infected with herpes virus. J. Gen. Microbiol. **19**:244–249.
52. TEAGUE, O., AND E. W. GOODPASTURE. 1923. Experimental herpes zoster. J. Med. Res. **44**:185–200.
53. WEISS, P. 1944. Damming of axoplasm in constricted nerve: a sign of perpetual growth in nerve fibers. Anat. Record **88**:464.
54. WEISS, P., AND H. B. HISCOE. 1948. Experiments on the mechanism of nerve growth. J. Exptl. Zool. **107**:315–395.
55. WEISS, P., A. C. TAYLOR, AND P. A. PILLAI. 1962. The nerve fiber as a system in continuous flow: microcinematographic and electronmicroscopic demonstrations. Science **136**:330.
56. WILDY, P., W. C. RUSSELL, AND R. W. HORNE. 1960. The morphology of herpes virus. Virology **12**:204–222.